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Genetic Analysis of Sex and Generation Differences in Plasma Lipid, Lipoprotein, and Apolipoprotein Levels in Adolescent Twins and Their Parents

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In a sample of Dutch families consisting of parents aged 35–65 years and their twin offspring aged 14–21 years, a significant difference between generations was observed in phenotypic variances and in genetic heritabilities for plasma levels of total cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, and apolipoproteins (apo) A1, A2, B, and E. For all traits parents were more variable than their offspring. This increase in phenotypic variance was best explained by a genetic model in which individual specific environmental variance increased with increasing age. Genetic variance was the same across generations for nearly all traits except triglycerides and apoE, for which a decrease in genetic variance was observed. This model led to large intergenerational differences in genetic heritabilities. Heritabilities for children were between 65 and 87%, while heritabilities for their parents were between 10 and 50%. No evidence was found for effects of a shared family environment.

Key words: heritability, cholesterol, triglycerides, HDL, LDL, apoA1, apoA2, apoB, apoE

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INTRODUCTION

Epidemiologic studies have shown that variation in plasma lipid, lipoprotein, and apolipoprotein levels is associated with the development of atherosclerosis. The association of coronary risk with an increased plasma total cholesterol level is well established, whereas the association with triglyceride levels remains controversial. Cholesterol and triglycerides are transported in plasma by lipoproteins. In individuals under 50 years of age elevated levels of low density lipoproteins (LDL) and depressed levels of high density lipoproteins (HDL) are strong predictors of atherosclerosis risk. In individuals over age 60 years LDL cholesterol levels become less and HDL cholesterol levels seem to become even more predictive for atherosclerosis risk [for reviews see Hegele and Breslow, 1987; Wallace and Anderson, 1987; Rader and Brewer, 1994]. Apolipoproteins are the protein constituents of lipoproteins and are themselves risk factors for coronary heart disease. Apolipoproteins (apo) A1 and A2 are the main and second most abundant proteins in HDL, apoB is the sole protein in LDL and also a major protein in very low density lipoprotein (VLDL), and apoE is a protein component of both VLDL and HDL. In several studies, plasma levels of apolipoproteins, especially elevated levels of apoB and depressed levels of apoA1 and apoA2, discriminated atherosclerotic patients from controls even better than plasma lipid levels [Avogaro et al., 1978; Sniderman et al., 1980; Fager et al., 1981; Maciejko et al., 1983; Kukita et al., 1984; Durrington et al., 1988].

There is evidence from numerous twin and family studies that quantitative variation in lipid and lipoprotein levels is partly genetically determined [reviewed in Iselius, 1979, 1988; Nora et al., 1991; Heller et al., 1993], while for apolipoproteins this evidence is less abundant. Based on published reports of family resemblance, Iselius [1979] estimated heritability for total cholesterol, triglycerides, HDL and LDL cholesterol to be around 50%, without much evidence for significant contributions of the the family environment. For apoA1 heritability estimates based on twin studies vary between zero and 100%. For apoA2 and apoB moderate to strong genetic influences have been found [reviewed in Iselius, 1988; Lamon-Fava et al., 1991; Rao and Vogler, 1994], while no twin or family studies of quantitative apoE levels are available [Moll, 1993].

It is well established that means and variances of most lipid, lipoprotein, and apolipoprotein parameters increase as people grow older [Wallace and Anderson, 1987; Reilly et al., 1990; Ericsson et al., 1991]. These age-related increases in phenotypic variance may be due to increases in genetic or environmental variance with increasing age, or both. Changes in the contributions of genetic and environmental factors may lead to changes in heritabilities with age, but little attention has been paid to changes in heritabilities of lipid, lipoprotein, and apolipoprotein levels over the lifespan.

To address this issue, we compared estimates for genetic and environmental variances in parents and their adolescent offspring for plasma levels of total cholesterol, triglycerides, LDL and HDL cholesterol, and apoA1, apoA2, apoB, and apoE. The offspring in this study consisted of male and female monozygotic (MZ) and dizygotic (DZ) twins.

SUBJECTS AND METHODS

Subjects

This study is part of a larger project in which cardiovascular risk factors were studied in 160 adolescent twin pairs and their parents. Addresses of twins (between 14 and 21 years of age) living in Amsterdam and neighboring cities were obtained from City Council population registries. Twins still living with both of their biological parents were contacted by letter. A family was included in the study if the twins and both parents complied. In addition, a small number of families who heard of the study from other twins also volunteered to participate.

Zygosity was determined by typing the following polymorphisms: ABO, MNS, P, Rhesus, Lutheran, Kell, Duffy, Kidd, Gm, Am, and Km. In addition, 36 pairs were typed by DNA fingerprinting [Jeffreys et al., 1985]. Three series of triplets were included by discarding the data from the middle child.

There were 35 monozygotic female pairs (MZF; average age 16.0 years, SD = 2.2), 35 monozygotic male pairs (MZM; average age 16.6 years, SD = 1.8), 30 dizygotic female pairs (DZF; average age 17.7 years, SD = 2.0), 31 dizygotic male pairs (DZM; average age 17.2 years, SD = 1.7), and 29 dizygotic opposite-sex pairs (DOS; average age years, 16.4, SD = 1.8). The average ages of fathers and mothers were 48.1 years (SD = 6.3) and 45.6 years (SD = 5.9), respectively.

Methods

EDTA blood was obtained between 8:30 and 10:30 AM by venipuncture after overnight fasting. Plasma was separated from cells after centrifugation for 10 min at 3,000 rpm. Part of the plasma was kept at 4°C for lipid determinations within the next 5 days. The remainder was frozen at −20°C for later use. Cholesterol and triglyceride levels were determined using enzymatic methods (CHOD-PAP kit number 236691 and GPO-PAP kit number 701904, Boehringer Mannheim, Germany). HDL cholesterol was measured after precipitation with phosphotungstate Mg^{2+} of VLDL, intermediate density lipoprotein (IDL), and LDL according to Lopes-Virella et al. [1977]. LDL cholesterol was calculated by the formula of Friedewald [Friedewald et al., 1972]. With this formula triglyceride concentrations must not exceed 4.52 mmol/l [Rifai et al., 1992]. There were no subjects with triglycerides above 4.07 mmol/l. ApoA1, apoA2, and apoB were quantified by radial immunodiffusion as described by Albers et al., [1976] and Havekes et al. [1981]. ApoE was quantified by enzyme-linked immunosorbent assays (ELISA) as described by Bury et al. [1986].

Statistical Analyses

Blood samples were collected over a 2-year period with an average of ten families coming to the laboratory on the same occasion. All data were corrected for any between occasions variation. Because the distribution of triglyceride levels was skewed, these data were logarithmically transformed. For each variable, the data were summarized into 4 × 4 (Father, Mother, Twin 1, Twin 2) variance-covariance matrices for each of the five sex by zygosity groups, i.e., families of MZ male and female twins and families of DZ male, female, and opposite-sex twins. Likewise, 4 × 1 matrices containing the means for each variable were constructed for the five family

groupings. These matrices were used to estimate means and standard deviations for fathers, mothers, boys, and girls under the constraint that these are equal across the five sex by zygosity groups, while taking into account the dependency between the observations. The effects of sex, generation, and zygosity on means, variances, and correlations between relatives were assessed by likelihood ratio χ^2 tests by comparing the fit of a model that constrained parameter estimates to be equals across groups to one which allowed them to vary. The chi-squared statistic is computed by subtracting the χ^2 for the full model from that for a reduced model. The degrees of freedom (df) for this test are equal to the difference between the df for the full and the reduced model [Neale and Cardon, 1992].

Biometrical model fitting was carried out on variance-covariance matrices of the five different family groupings. Genetic models specified variation in phenotype to be due to genotype and environment. Sources of variation considered were G, additive genetic variation; C, common or shared family environment; and E, a random environmental deviation that is not shared by family members. Their influence on the phenotype is given by parameters h, c, and e, which are equivalent to the standardized regression coefficients of the phenotype on G, C, and E, respectively. The proportion of variance due to each source is the square of these parameters. Three different models were examined for each variable:

A. Full model in which estimates for h, c, and e are allowed to differ in magnitude between males and females, or between parents and offspring.
B. Scalar model in which heritabilities are constrained to be equal across sexes or generations, but in which total variances may be different. In the scalar model, the variance components for females, e.g., are constrained to be equal to a scalar multiple β, of the male variance components, such as $h_f^2 = \beta h_m^2$, $c_f^2 = \beta c_m^2$, and $e_f^2 = \beta e_m^2$. As a result, the standardized variance components (such as heritabilities) are equal across sexes, even though the unstandardized components differ [Neale and Cardon, 1992].
C. Constrained model in which one or all parameter estimates for h, c, and e are constrained to be equal in magnitude across sexes or generations.

Parameters h, c, and e were estimated by maximum likelihood, using the computer program LISREL7 [Jöreskog and Sörbom, 1988]. Goodness-of-fit was assessed by likelihood ratio χ^2 tests. The overall χ^2 tests the agreement between the observed and the predicted variances and covariances in the 5 family groupings. A large χ^2 indicates a poor fit, while a small χ^2 indicates that the data are consistent with the model. Submodels were compared by hierarchic χ^2 tests. The scalar model (B) is a submodel of the full model (A) and the constrained model (C) is nested under B.

RESULTS

Descriptive Statistics

Table I gives means and standard deviations for all variables and χ^2 tests of sex and generation differences in means and variances. There were significant differences in means between parents and offspring for all variables (Table IA, χ^2 difference for 2 df larger than 5.99). Within generations, girls had significantly higher values than boys for total and HDL cholesterol and apoA1 and apoE concentrations (χ^2

TABLE I. Maximum Likelihood Estimates of Means (A) and Standard Deviations (B) for Twins and Parents and χ^2 Tests of Sex and Generation Differences*

	TC	LOGTG	HDL	LDL	ApoA1	ApoA2	ApoB	ApoE
				A. Means				
Sons	4.12	−0.20	1.24	2.59	134.31	58.10	78.83	6.08
Daughters	4.37	−0.19	1.37	2.68	142.63	57.50	78.59	7.45
Fathers	5.87	0.09	1.14	4.10	140.16	62.93	112.09	7.71
Mothers	5.61	−0.07	1.41	3.78	155.20	63.70	102.45	7.92
χ^2 test of sex differences in mean (df = 1)								
Twins	7.92[a]	0.67	19.15[a]	0.44	12.52[a]	0.35	0.02	23.25[a]
Parents	6.23[a]	55.16[a]	77.27[a]	11.74[a]	49.72[a]	0.53	29.56[a]	0.54
χ^2 test of generation differences in means (df = 2)								
	>100[a]	>100[a]	15.39[a]	>100[a]	54.61[a]	84.93[a]	>100[a]	54.77[a]
				B. Standard Deviations				
Sons	0.63	0.16	0.21	0.61	13.92	6.57	14.38	2.07
Daughters	0.75	0.15	0.27	0.70	21.64	8.02	17.67	2.46
Fathers	1.02	0.21	0.28	0.95	21.65	9.94	21.62	2.31
Mothers	1.07	0.18	0.30	1.02	19.87	9.64	20.44	2.80
χ^2 test of sex differences in variances (df = 1)								
Twins	7.09[a]	0.34	10.48[a]	2.70	30.22[a]	6.05[a]	6.98[a]	4.65[a]
Parents	0.70	3.68	0.79	0.80	1.16	0.14	0.54	5.60
χ^2 test of generation differences in variances (df = 2)								
	48.32[a]	14.66[a]	12.32[a]	45.81[a]	23.34[a]	26.06[a]	21.22[a]	4.18

*TC, total cholesterol (mmol/l); LOGTG, logarithmically transformed triglyceride (mmol/l); HDL, high density lipoprotein cholesterol (mmol/l); LDL, low density lipoprotein cholesterol (mmol/l); ApoA1, apolipoprotein A1 (mg/dl); ApoA2, apolipoprotein A2 (mg/dl); ApoB, apolipoprotein B (mg/dl); ApoE, apolipoprotein E (mg/dl).
[a]Significant χ^2.

difference for 1 df larger than 3.84). Fathers had higher mean values than mothers for risk-enhancing factors, triglycerides, total and LDL cholesterol, and apoB. For HDL cholesterol and apoA1, fathers had significantly lower mean values than mothers. There were no differences between fathers and mothers for apoA2 and apoE. Table IB shows that there were significant differences in variances between the two generations for all variables except apoE. Within generations, girls were more variable than boys for almost all variables except triglycerides and LDL. In the parental generation, fathers were more variable than others for apoE only.

Genetic Analyses

Table II lists familial correlations for twins, spouses, and parents and offspring. MZ twin correlations were higher than the corresponding DZ correlations for all variables. Tests for homogeneity of twin correlations across sexes showed no differences between MZM and MZF correlations, nor between the three DZ correlations (critical χ^2 value for 3 df is 7.81). Spouse correlations were not significantly different from zero except for total cholesterol, LDL, and apoB. Parent-offspring correlations were estimated separately for fathers and mothers with their sons and daughters, but χ^2 tests showed that these correlations did not depend on either the sex of the parent or the offspring.

TABLE II. Maximum Likelihood Estimates of Familial Correlations*

	TC	LOGTG	HDL	LDL	ApoA1	ApoA2	ApoB	ApoE
MZF	0.737	0.772	0.735	0.789	0.725	0.786	0.785	0.856
DZF	0.566	0.212	0.379	0.460	0.521	0.540	0.498	0.265
MZM	0.864	0.574	0.689	0.848	0.838	0.843	0.829	0.887
DZM	0.279	0.464	0.472	0.352	0.400	0.346	0.562	0.378
DOS	0.299	0.007	0.449	0.397	0.303	0.050	0.669	0.335
Spouses	0.206	0.065	0.070	0.209	0.124	0.078	0.313	0.23
Father-son	0.265	0.146	0.148	0.332	0.240	0.076	0.242	0.251
Father-daughter	0.218	0.085	0.230	0.227	0.363	0.273	0.303	0.165
Mother-son	0.372	0.144	0.370	0.349	0.353	0.307	0.354	0.394
Mother-daughter	0.233	0.201	0.238	0.273	0.304	0.210	0.344	0.193
All MZ	0.804	0.669	0.711	0.822	0.775	0.814	0.808	0.871
All DZ	0.381	0.255	0.433	0.409	0.360	0.334	0.553	0.330
Parent-child	0.282	0.126	0.231	0.301	0.277	0.193	0.314	0.245
χ^2 test of sex differences in twin correlations (df = 3)	5.72	7.04	0.40	1.20	3.50	4.92	1.44	0.18
χ^2 test of sex differences in twin correlations (df = 3)	2.43	0.89	3.94	1.47	1.54	3.74	1.32	4.88
χ^2 test of zero spouse correlation (df = 1)	6.73[a]	0.66	0.76	6.91	2.40	0.94	15.99	0.08

*Abbreviations are defined in Table I.
[a]Significant χ^2.

Results of biometrical model fitting to variance-covariance matrices of twins are presented in Table III. No models are shown that excluded genetic influences on the dependent variables, because these always showed a poor fit. Models fitted badly when parameter estimates were constrained to be equal in males and females without recognizing the sex differences in variances for most variables (Table III). Only for triglycerides and LDL a simple GE model without sex differences showed a good fit to the data. For total cholesterol, HDL, apoA1, apoA2, and apoE, a scalar model in which heritabilities were constrained to be equal for males and females gave the best fit and the most parsimonious account of the data (Table IIIB). The only variable that showed a significant influence of shared family environment in both sexes was apoB. At the bottom of Table III, heritability estimates based on the best fitting model for each variable are given.

Table IV shows χ^2 values and associated probabilities for three different genetic models of familial resemblance between parents and offspring. In the first model (Table IVA) separate genetic and environmental variances in the two generations were estimated, in the second model (Table IVB) heritabilities were constrained to be equal across generations while the total trait variances were allowed to differ between generations, and in the third model (Table IVC) the genetic variance was constrained to be the same across generations, while the environmental variances for each trait could be different in parents and offspring. For nearly all variables, i.e., total, HDL and LDL cholesterol, apoA1, apoA2, and apoB, the best fitting model specified genetic variance to be equal across generations. The larger variance that was observed for these variables in the parental generation appeared to be due to an increase in

TABLE III. Biometrical Model Fitting to Data From Twins Only: Test of Sex Differences in Genetic Architecture*

	TC	LOGTG	HDL	LDL	ApoA1	ApoA2	ApoB	ApoE
	Chi-Squared Statistics and Probability Levels							
A. Sex differences								
GEC	4.90	11.87	19.87	6.50	14.82	5.49	12.45	5.15
(df = 9)	(0.843)	(0.221)	(0.019)	(0.689)	(0.096)	(0.790)	(0.189)	(0.821)
GE	7.19	15.43	20.80	6.89	15.85	9.93	16.90	5.15
(df = 11)	(0.784)	(0.164)	(0.036)	(0.808)	(0.147)	(0.537)	(0.111)	(0.924)
B. Scalar model								
GEC	10.66	16.86	20.12	7.82	18.48	10.48	12.83	5.46
(df = 11)	(0.472)	(0.112)	(0.044)	(0.730)	(0.071)	(0.488)	(0.305)	(0.905)
GE	10.69	16.86	21.00	7.90	18.48	10.48	17.05	5.46
(df = 12)	(0.555)	(0.155)	(0.050)	(0.793)	(0.102)	(0.574)	(0.148)	(0.941)
C. No differences								
GEC	17.75	17.09	30.60	10.52	48.69	16.33	19.81	10.35
(df = 12)	(0.123)	(0.146)	(0.002)	(0.570)	(0.000)	(0.176)	(0.071)	(0.585)
GE	18.04	17.09	31.19	10.67	48.69	16.33	24.56	10.35
(df = 13)	(0.156)	(0.195)	(0.003)	(0.638)	(0.000)	(0.232)	(0.026)	(0.665)
	Heritabilities (%) Based on Best Fitting Model							
	80	65	71	82	78	81	48[a]	87

*The most parsimonious model for each trait in underlined. Abbreviations are defined in Table I.
[a]For apoB the estimate for c^2 was 33%.

environmental variance that is not shared between family members. For triglycerides and apoE, the environmental variance in parents was also larger than in children, but additionally, the genetic variance was significantly smaller in parents than in children. Resemblance between spouses for total and LDL cholesterol and apoB was attributed to the environmental component.

Because the analyses of the twin data had indicated significant evidence for shared environmental influences on apoB, such a component was also estimated in the analysis of the parent-offspring data. No improvement in fit was seen, and the estimate for shared environment was not significantly different from zero. Separate heritability estimates for parents and offspring based on the best fitting model are given at the bottom of Table IV.

DISCUSSION

We observed in a group of Dutch families consisting of parents aged 35–65 years and their offspring aged 14–21 years a significant difference between generations in phenotypic variances for total cholesterol, triglycerides, HDL and LDL cholesterol, and apoA1, apoA2, and apoB. For all of these traits parents were more variable than their offspring. ApoE was the only trait that did not show this increase in phenotypic variance with increasing age. Reilly et al. [1990], in a large study of three generations participating in the Rochester Family Heart Study, also observed significant differences among generations in variances for total cholesterol, triglycerides, HDL and LDL cholesterol, and apoA1, but not for apoA2. As in our study, no differences

TABLE IV. Biometrical Model Fitting to Parent-Twin Data Test of Generation Differences in Genetic Architecture*

	TC	LOGTG	HDL	LDL	ApoA1	ApoA2	ApoB	ApoE
	Chi-Squared Statistics and Probability Levels							
A. Generation differences	52.12	42.55	78.95	49.25	63.58	58.95	57.09	49.38
df	44	46	45	45	45	45	44	44
P	(0.187)	(0.618)	(0.001)	(0.307)	(0.035)	(0.079)	(0.089)	(0.267)
B. Scalar model	58.70	57.14	89.92	55.71	72.88	87.45	63.31	77.38
df	45	47	46	46	46	46	45	45
P	(0.083)	(0.148)	(0.000)	(0.155)	(0.007)	(0.000)	(0.037)	(0.002)
C. Equal genetic variance	53.02	49.60	79.44	49.46	63.84	61.79	57.25	56.51
df	45	47	46	46	46	46	45	45
P	(0.192)	(0.370)	(0.002)	(0.337)	(0.042)	(0.060)	(0.104)	(0.117)
	Heritabilities (%) Based on Best Fitting Model							
Parents	29	10	35	37	35	50	38	31
Offspring	81	65	71	82	78	80	81	87

*Models for TC, HDL, apoA1, apoA2, and apoB include parameter for sex differences in offspring; models for apoE include parameter for sex differences in parents and offspring; and models for TC, LDL, and apoB include extra parameter for spouse resemblance. The most parsimonious model for each trait is underlined. Abbreviations are defined in Table I.

among generations in apoE variances were found. The significant differences in variance across generations were attributable to an increase in variance with increasing age. Reilly et al. [1990] hypothesized that these increases in phenotypic variances in the older generation might be due to the cumulative effects of exposure to environmental factors.

We found evidence in our study that for most lipids, lipoproteins, and apolipoproteins environmental variance indeed increases with increasing age. This leads to a pattern of relatively low correlations between parents and offspring compared to relatively high correlations among siblings. Also, the larger amount of environmental variance for most measures in the parental generation leads to marked differences in heritabilities between generations for plasma lipid, lipoprotein, and apolipoprotein concentrations. Heritabilities for total cholesterol, triglycerides, and LDL and HDL cholesterol were 29, 10, 37, and 37% in parents and 81, 65, 71, and 82% in children. For apoA1, apoA2, apoB, and apoE heritabilities were 35, 50, 38, and 31% in parents and 78, 80, 81, and 87% in children. The best fitting model for these traits indicated that the influence of genetic factors was of equal magnitude in parents and children (except for triglycerides and apoE, for which genetic variance in parents was lower) and that the decreases in heritability were caused by an increase in environmental variance in the older generation.

The analysis of sex differences indicated that heritabilities in males and females were of the same magnitude. In the analysis of the twin data no sex differences in heritabilities for any of the traits were found. The larger variance for several traits in female twins could be accounted for by a scalar model in which heritabilities were constrained to be the same for both sexes. These findings seem consistent with results from other studies. For example, Towne et al. [1993] examined sex differences in 13 quantitative measures of lipids, lipoproteins, and apolipoproteins in 25 kindreds. For

the 6 variables that overlapped with our study, the only sex difference in heritability was for triglycerides. Bodurtha et al.. [1991] studied genetic influences on cholesterol and some subfractions in early-pubertal twins. They found a somewhat larger heritability in females (80 vs. 71%) for total cholesterol but not for HDL and LDL cholesterol or triglycerides.

The absence of sex differences in heritabilities is supported by the fact that we did not find differences in magnitude between father-offspring and mother-offspring correlations for any of the traits studied. Rao et al. [1979] found higher mother-offspring than father-offspring correlations for several lipid and lipoprotein traits in families participating in the Honolulu Heart Study. Chung [1984] also reported higher correlations in mothers and their children below the age 20 years than in fathers and these children for subjects participating in the Cincinnati Lipid Family Study, although no significant maternal effect was found in a path analytic model. Chung [1984] suggests a stronger environmental influence of mothers on children, especially since mother-child resemblance decreased for older offspring. However, no evidence for shared family environmental influences was found in our study, although the sample consisted entirely of parents and children living in the same household. In both sexes and both generations a simple model that allowed for additive genetic influences and individual specific environmental effects gave the most parsimonious account of the data. A significant correlation between spouses was seen for total and LDL cholesterol concentrations and for apoB levels. Coresh et al. [1992] also observed a significant spouse correlation for apoB, but did not report its size.

The heritabilities that were obtained for the twin offspring are somewhat higher than those commonly found in other studies. One of the reasons for this finding may be that the twins who participated in our study were relatively young. Bodurtha et al. [1991] obtained similarly high heritabilities for total, HDL and LDL cholesterol, and triglycerides in their study of young twins. The lower heritability in the parental generation is a very consistent finding across all lipid, lipoprotein, and apolipoprotein traits. In contrast, no intergenerational differences in heritability were observed in this same sample for plasma lipoprotein(a) concentrations [Boomsma et al., 1993a] or for plasma levels of histidine-rich glycoprotein (HRG), a potential risk factor for thrombosis [Boomsma et al., 1993b]. Heller et al. [1993] observed in two Swedish twin cohorts that the effect of genetic factors markedly decreased with age for total cholesterol, triglycerides, and apoB, but not for HDL and apoA1. However, the heritability estimates in the youngest cohort (52–65 years) were higher than the estimates we found in the parental generation. Rao et al. [1979] also obtained evidence for intergenerational differences in genetic heritability for VLDL, triglycerides, and total and HDL cholesterol. However, for triglycerides genetic heritability was greater in parents than in offspring. Chung [1984] and Hamsten et al. [1986] did not find intergenerational differences in heritability for total cholesterol, LDL, HDL, or triglycerides. Hamsten et al. [1986] also did not observe differences for apoA1, and apoA2, but found a significantly lower heritability for apoB in parents than in offspring. However, these heritabilities were obtained from data on nuclear families by analyzing correlations instead of variances and covariances and results may therefore not be directly comparable.

Our findings suggest that heritabilities for risk factors for coronary heart disease decrease as people grow older. This decrease in heritability is mainly due to an in-

crease in environmental variance with increasing age. In contrast, for total, HDL, and LDL cholesterol and apoA1, apoA2, and apoB, the influence of genetic factors seems to be stable from adolescence through adulthood. This model is based on the assumption that the same genes are expressed in parents and their offspring, i.e., that the genetic correlation between genetic effects expressed during adolescence and adulthood equals unity. To test this assumption longitudinal data from genetically informative subjects are needed. Williams and Wijesiri [1993] analyzed longitudinal data on total, LDL, and HDL cholesterol and triglycerides from the NHLBI veteran twin study. Between 48 and 63 years of age a high stability in the expression of genetic factors was found. However, the age range of the veteran sample is not directly comparable to the age range of adolescents and their parents participating in our study. An alternative to a longitudinal study would be to augment the present design with twins of the same age as the parents from this study. Heritabilities then can be estimated for each generation separately, based on the information available from adolescent and adult twins. If these heritabilities are known, the observed parent-offspring correlation can be used to estimate the correlation between genetic values in adolescence and adulthood. Likewise, the stability of environmental effects can be examined. A project is currently underway in which in a sample of middle-aged twins the same variables are assessed that were measured in the adolescent twins and their parents. For blood pressure, a simultaneous analysis of the data from these groups showed that the increase in variance in systolic and diastolic blood pressure with age was explained by an increase in environmental variance in males and by an increase in both genetic and environmental variance in females [Snieder et al., 1995]. If the increase in variance in the lipid, lipoportein, and apolipoprotein phenotypes in the older generation is confirmed to be due to an increase in environmental variance, then this finding could influence future strategies for identifying genes that are associated with quantitative variation in these traits. A major determinant of power to detect quantitative trait loci is the total heritability of a trait [Risch and Zhang, 1995]. Our results suggest that to detect such loci for lipids, lipoproteins, and apolipoproteins the best strategy might be to study relatively young subjects.

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